Remarks

Reconsideration of this Application is respectfully requested.

Claims 75-78, 81-84, 86-103, 105-107 and 109-145 are pending in the application, with claims 75, 102, 103 and 125 being the independent claims.

A request for continued examination (RCE) is being filed concurrently herewith. Therefore, the finality of the Office Action dated May 3, 2002 should be withdrawn and this Supplemental Reply should be entered and considered. *See* 37 C.F.R. § 1.114(d).

Based on the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding rejections and that they be withdrawn.

Claim Rejections Under 35 U.S.C. § 112, First Paragraph

A. Written Description

Claims 75-79, 81-84, 86-101, 103, 105-107 and 109-136 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. *See* Paper No. 22, pages 3-4; *see also* Paper No. 26, pages 2-4. Applicants respectfully traverse this rejection for the reasons set forth in Applicants' previous reply. *See* Amendment and Reply filed November 4, 2002, pages 15-17. In addition, Applicants present the following remarks in support of their position that the specification provides an adequate description of the claimed subject matter.

To satisfy the written description requirement of 35 U.S.C. § 112, first paragraph, an Applicant must convey with reasonable clarity to those skilled in the art that, as of the effective filing date, the Applicant was in possession of the invention. *See Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1560, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991). The Federal Circuit has recently indicated that, in the context of claims to genetic material, functional descriptions may satisfy the written description requirement. *See Enzo Biochem, Inc. v. Gen-Probe Inc.*, 296 F.3d 1316, 1324 (Fed. Cir. 2002) ("It is not correct, however, that all functional descriptions of genetic material fail to meet the written description requirement.") The principle inquiry is whether the disclosed functional characteristics are coupled with a known or disclosed correlation between function and structure; if so, the written description requirement is satisfied. *See id.*

Applicants' claims, as currently presented, are directed to, or involve the use of, nucleic acid molecules which comprise a first open reading frame which encodes a non-cytopathic, temperature-sensitive alphaviral replicase, wherein non-cytopathicity and temperature sensitivity are conferred by one or more mutations in the genes encoding the non-structural proteins of said replicase. Based on the Federal Circuit's current interpretation of the written description requirement, Applicants believe that the present claims are adequately described under § 112, first paragraph.

First, the present specification (along with the references cited therein) provides sufficiently detailed relevant identifying characteristics of the non-cytopathic, temperature-sensitive alphaviral replicases encompassed by or used in the practice of the present claims. For instance, Dryga *et al.*, *Virology 228*:74-83 (1997), which is cited and incorporated by reference in the specification at page 22, line 7, indicates that a non-cytopathic alphaviral replicase will enable the establishment of persistent infected cultures of host cells.

Furthermore, the specification provides a detailed discussion of the various biological attributes exhibited by temperature-sensitive alphaviral replicases. *See, e.g.*, specification at page 22, line 26 through page 23, line 13.

It is made clear in the specification that non-cytopathicity and temperature sensitivity can be conferred by one or more mutations in the genes encoding the non-structural proteins ("nsPs") of the replicases. *See* specification at page 21, line 23 through page 22, line 25. As an example, the specification notes that mutations in the nsP2 and nsP4 genes of the Sindbis virus replicase (specifically, a P726S nsP2 mutation and a G153E nsP4 mutation) render the polymerase non-cytopathic and temperature sensitive. *See* specification at page 21, lines 25-26 and at page 22, lines 17-18. In view of the ease with which genes encoding alphaviral nsPs can be mutated and the ease with which the corresponding alphaviral replicases can be screened for non-cytopathicity and temperature-sensitivity, Applicants assert that the relevant identifying characteristics of the alphaviral replicases of the invention are adequately disclosed in the present specification. The ability of those skilled in the art to obtain non-cytopathic, temperature-sensitive alphaviral replicases is described in the Declaration of Dr. Sondra Schlesinger Under 37 C.F.R. § 1.132, submitted herewith and discussed in more detail below.

Second, there is a known correlation between: (a) the "structural" attributes of the nucleic acid molecules that encode alphaviral nsPs, and (b) the function of alphaviral replicases. This correlation is evidenced, for example, by the numerous described mutations in alphaviral nsP genes that cause temperature-sensitivity or non-cytopathicity. Examples of such mutations are described in Suopanki *et al.*, *J. Gen. Virol. 79*:309-319 (1998) (copy attached as Exhibit 1); LaStarza *et al.*, *J. Virol. 68*:5781-5791 (1994) (copy attached as Exhibit 2); Wang *et al.*, *J. Virol. 65*:985-988 (1991) (copy attached as Exhibit 3); Shirako

and Strauss, *Virology 177*:54-64 (1990) (copy attached as Exhibit 4); Hardy *et al.*, *Virology 177*:199-208 (1990) (copy attached as Exhibit 5); Hahn *et al.*, *J. Virol. 63*:3142-3150 (1989) (copy attached as Exhibit 6); Sawicki and Sawicki, *J. Virol. 67*:3605-3610 (1993) (copy attached as Exhibit 7); Hahn *et al.*, *J. Virol. 63*:1194-1202 (1989) (copy attached as Exhibit 8); Shirako and Strauss, *J. Virol. 72*:2310-2315 (1998) (copy attached as Exhibit 9); Lemm *et al.*, *J. Virol. 64*:3001-3011 (1990) (copy attached as Exhibit 10); Sawicki *et al.*, *Virology 174*:43-52 (1990) (copy attached as Exhibit 11); and Dryga *et al.*, *Virology 228*:74-83 (1997) (copy submitted as document AS6 in the Information Disclosure Statement filed on June 28, 1999). In addition, subsequent to the effective filing date of the application, additional mutations causing temperature sensitivity or non-cytopathicity have been described. *See, e.g.*, Perri *et al.*, *J. Virol. 74*:9802-9807 (2000) (copy attached as Exhibit 12). Many of the mutations described in the foregoing articles were created deliberately by researchers who mutagenized the nsP genes and screened for the desired phenotypes. Thus, the large number of mutations in alphaviral nsP genes that are known to cause temperature sensitivity or non-cytopathicity supports the notion that there is a known correlation between mutations in alphaviral nsP genes and non-cytopathic and temperature-sensitive phenotypes exhibited by the corresponding alphaviral replicases.

Another indication of the correlation between the structure and function of the nucleic acid molecules of the present invention is the high level of sequence homology that exists among the nsPs of alphaviruses. *See* Applicants' Amendment and Reply filed on July 31, 2001, page 10. To illustrate more particularly the high level of sequence homology that exists among the nsPs of alphaviruses, Applicants submit herewith a table (Exhibit 13)

which shows the percent amino acid sequence identity and similarity[1] that exists between the nsPs of the following alphaviruses: O'nyong-nyong virus (ONG), Ross River virus (RRV), Semliki Forest virus (SFV), Sindbis virus (SinV), Venezuelan equine encephalitis virus (VEEV) and Western equine encephalomyelitis virus (WEEV). Applicants also submit herewith individual amino acid sequence alignments[2] comparing the sequences of alphaviral nsP1, nsP2, nsP3 and nsP4 proteins (Exhibits 14, 15, 16 and 17, respectively). Finally, a phylogenetic tree is presented (Exhibit 18) showing the evolutionary relationship among the nsP2 and nsP4 proteins from various alphaviruses. Although these sequence comparisons involve amino acid sequences, they necessarily reflect the degree of correlation that exists among the alphaviral nsP genes at the nucleic acid level.

In view of the numerous alphaviral nsP mutations described in the art which confer temperature sensitivity or non-cytopathicity, and the high level of sequence homology that exists among the nsPs from various alphaviruses, Applicants submit that there is a known correlation between the functional characteristics of the alphaviral replicases of the present invention (temperature sensitivity and non-cytopathicity) and their structural attributes (one or more mutations in the genes encoding the non-structural proteins of the replicases). One of ordinary skill in the art could therefore envision (and create) multiple species of alphaviral replicases that are encompassed by the present claims. That is, a person of ordinary skill in the art would conclude that Applicants were in possession of the claimed subject matter. Accordingly, Applicants respectfully request that the rejection of claims 75-79, 81-84, 86-

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[1] Calculation of percent identity and percent similarity was performed using the BLAST-2 Sequences program.

[2] Alignments were performed using the ClustalW program. Identical residues in all sequences are indicated with an asterisk (*), conserved substitutions are indicated with a colon (:) and semi-conserved substitutions are indicated with a period (.).

101, 103, 105-107 and 109-136 under 35 U.S.C. § 112, first paragraph, for insufficient written description, be reconsidered and withdrawn.

B. Enablement

Claims 75-79, 81-84, 86-101, 103, 105-107 and 109-136 were rejected under 35 U.S.C. § 112, first paragraph, because, according to the Examiner, "[t]he specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. . ." *See* Paper No. 22, page 8; *see also* Paper No. 26, pages 5-6. The basis for this rejection is the Examiner's position that it is difficult to predict the relationship between nucleic acid mutations and protein function. *See, e.g.*, Paper No. 22, page 9 ("it is not currently possible to accurately predict the effects of mutations on the functions of proteins.")

As noted in the Amendment and Reply filed on November 4, 2002, the construction and selection of nucleic acid molecules that encode temperature-sensitive, non-cytopathic RNA-dependent RNA polymerases (*i.e.*, replicases) would not require one of ordinary skill in the art to make predictions regarding the effects of mutations on protein function. Rather, the creation of temperature-sensitive, non-cytopathic alphaviral replicases requires only that a skilled artisan engage, for example, in the mutagenesis of a nucleic acid encoding an alphaviral replicase and then screen for those molecules which possess the desired phenotypes (temperature sensitivity and non-cytopathicity).

As asserted in Applicants' previous Reply, such a mutagenesis and screening approach would be considered routine experimentation in the art. There are many examples in the art of temperature sensitive or non-cytopathic alphaviral replicases that have been created by such a strategy. *See, e.g.*, LaStarza *et al.*, *J. Virol.* *68*:5781-5791 (1994) (copy

attached as Exhibit 2) (describing the construction of random linker insertion mutations in Sindbis virus nsP3 to generate temperature sensitive mutants); Shirako and Strauss, *Virology 177*:54-64 (1990) (copy attached as Exhibit 4) (describing mutations created in the penultimate Gly in Sindbis virus nsP1 which resulted in temperature sensitivity); Shirako and Strauss, *J. Virol. 72*:2310-2315 (1998) (copy attached as Exhibit 9) (describing N terminal mutations made in the nsP4 gene of Sindbis virus which caused temperature sensitivity); and Perri *et al.*, *J. Virol. 74*:9802-9807 (2000) (copy attached as Exhibit 12) (describing the isolation of non-cytopathic Sindbis virus replicase mutants created by random mutagenesis).

As additional evidence that a person of ordinary skill in the art would have been able to obtain nucleic acid molecules encoding temperature-sensitive, non-cytopathic alphaviral replicases using only routine experimentation in view of the teachings of the specification, Applicants submit herewith a Declaration of Professor Sondra Schlesinger Under 37 C.F.R. § 1.132. As confirmed by Professor Schlesinger's Declaration, a person of ordinary skill in the art would not have needed to predict the effects of mutations on protein function in order to produce temperature-sensitive, non-cytopathic alphaviral replicases. Rather, Professor Schlesinger confirms that one of ordinary skill in the art, upon reading the present specification, would have been able to -- without undue experimentation -- use a mutagenesis and screening process to produce additional nucleic acid molecules encoding temperature-sensitive, non-cytopathic alphaviral replicases. One exemplary screening strategy that would have been contemplated by persons of ordinary skill in the art is presented in Professor Schlesinger's declaration (paragraph 5). Professor Schlesinger also confirms that persons of ordinary skill in the art, at the time the application was filed,

typically engaged in mutagenesis and screening strategies to produce nucleic acid molecules encoding proteins with specific desired phenotypes.

Thus, the creation of temperature-sensitive, non-cytopathic alphaviral replicases could have been readily accomplished using well-known mutagenesis and screening methods. The evidence presented above demonstrates that persons of ordinary skill in the art would have been prepared and willing to engage in such a screening strategy. As noted by the Federal Circuit, screening – even screening that involves the generation of numerous negative outcomes – is not deemed undue experimentation when those skilled in the art typically engage in such screening. *See In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). The references cited above and the Declaration of Professor Schlesinger show that persons of ordinary skill in the art typically screened through numerous mutant proteins for those that possessed particular desired phenotypes, *e.g.*, temperature sensitivity and non-cytopathicity. Under *Wands*, the production of nucleic acid molecules encoding temperature-sensitive, non-cytopathic alphaviral replicases for use with the present invention would not involve undue experimentation.

Since the specification, in conjunction with the knowledge possessed by persons of ordinary skill in the art, fully enables the creation of additional nucleic acid molecules encoding temperature-sensitive, non-cytopathic alphaviral replicases, Applicants respectfully request that the rejection of claims 75-79, 81-84, 86-101, 103, 105-107 and 109-136 under 35 U.S.C. § 112, first paragraph, for lack of enablement, be reconsidered and withdrawn.

Conclusion

Applicants respectfully request that the Examiner reconsider all presently outstanding rejections and that they be withdrawn. Applicants believe that the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Supplemental Reply is respectfully requested.

Respectfully submitted,

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